UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P O Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,012	10/22/2003	Ole Buchardt	1SIS-5299	5682

32650 7590 04/22/2011
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
BORIN, MICHAEL L	
ART UNIT	**PAPER NUMBER**
1631	

NOTIFICATION DATE	DELIVERY MODE
04/22/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	10/691,012	BUCHARDT ET AL.	
	Examiner	Art Unit	
	MICHAEL BORIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/07/2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-36,38-41,43-45 and 47-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36,38-41,43-45 and 47-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other _____

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/07/2011 has been entered.

Status of Claims

Claims 34-36,38-41,43-45,47-73 are pending. The base claims 34,41,48,58,65 are amended to specify that the nucleic acid oligomer contains sequence of aza-linked ligands.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-36,38-41,43-45,47-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claims 34,41,48,58,65 are amended to specify that the nucleic acid oligomer contains sequence of aza-linked ligands (emphasis added). Review of specification indicates that there are only two references to are amended to specify that the nucleic acid oligomer contains sequence of aza linkage with respect to linking ligands to backbone. Summary section, p. 7, lines 25-26, informs that "the invention generally comprise ligands linked to a peptide backbone via an aza nitrogen". Further, p. 9, last paragraph, informs that

The peptide nucleic acids of the invention differ from those disclosed in WO 86/05518 in that their recognition moieties are attached to an aza nitrogen atom in the backbone, rather than to an amide nitrogen atom, a hydrazine moiety or a carbon atom in the backbone

However, looking at formulas of products of the invention, general formula I (p. 8) or formula III of preferred compounds (p. 10), these formulas do not encompass presence of aza nitrogen in the backbone. "Aza" indicates presence of -N=N- moiety in the backbone. However, permutations of values of A -B-D-G-C- moieties comprising the backbone does not produce an -N=N- moiety. Nor there is an -N=N- moiety obtainable from permutation of values for A1-An linkers (even though the specification is clear in defining that the aza- moiety in the backbone, not in the linker). Nor there are aza-linkages in Formula3 or Figure 1(B) describing preferred embodiments. Nor there are any examples in the specification

demonstrating aza-linked ligands. Therefore, it is not clear what bonding constitutes aza-linkage for ligands.

Clarification is requested.

Claim Rejections - 35 USC § 112, first paragraph (enablement).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-36,38-41,43-45,47-73 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for extra-cellular administration of the oligomers from the broad genus of a "polyamide nucleic acid oligomer containing neutral amide backbone linkages", does not reasonably provide enablement for *in vivo* extracellular administration that produces an intracellular biological response (such as modulation of protein expression).

The rejection is maintained for the reasons of record and further in view of the responses to applicant arguments presented following the rejection.

The claims are directed to *in vivo* administration of a broad range of agents addressed as "polyamide nucleic acid oligomer containing neutral amide backbone linkages which is complimentary to a target nucleic acid". In all claimed embodiments said agent is required to interact with the target nucleic acid; since the target nucleic acid is located intracellularly, said agent has to be able to get inside a cell - and this is the main issue of enablement - to be able to "engender a biological response associated with target in a sequence specific manner", as recited in claim 34. All independent claims maintain the above requirement and differ in that they are directed to:

- treating living cells comprising extracellular administering to the cells (claim 34);
- treating a mammal comprising extracellularly administering to the mammal (claim 41);
- administering to living cells (claim 48);
- administering to a mammal (claim 58)
- administering to a organism to specifically bind to DNA or RNA (claim 61)

The only working example in the specification addressing the claimed effect on target nucleic acids in cells is example 70 (p. 103). Example 70 describes inhibition of expression of E2 mRNA of papilloma virus. The deficiencies of this example with regard to the claimed subject matter are the following:

1. Example 70 describes *in vitro*, not *in vivo* administration
2. Example 70 addresses peptide nucleic acid (PNA), which is a narrow embodiment, not a "polyamide nucleic acid oligomer containing neutral amide backbone linkages" as broadly claimed;
3. Example 70 is a prophetic experiment which lacks any teaching of an actual PNA

Paragraphs [0156]-[0163] (pages 36-38) address "therapeutic use" of the subgenus of PNAs, and inform that PNAs can be formulated in a conventional pharmaceutical composition, administered in a number of conventional ways, such as topical, intravenous, etc., and that such administration would encompass treatment of live cells.

While the only guidance from the above section of specification is that the PNAs can be administered *in vivo* as conventional pharmaceutical formulations, there is no guidance in the specification regarding *in vivo* delivery of PNAs into cells, and furthermore, regarding delivering agents other than PNAs; i.e. those selected from a broad genus of "polyamide nucleic acid oligomers" .

With regard to *in* vivo delivery of peptide nucleic acids (PNAs) into cells, there is no guidance in the prior art on how to administer *in vivo* "polyamide nucleic acid oligomers" so as to exert the claimed specific intracellular effect of "engendering a biological response associated with target in a sequence specific manner". Applicant's own publications, published long after the effective filing date of the instant application, emphasize the unpredictability of the art. The following is a review of said applicant's "after-filing" publications:

A. In 1994 Nielsen et al. (3 of 4 inventors of the instant application) published "Peptide Nucleic Acids (PNA), A DNA Mimic with a Peptide Backbone." At pages 5-6 it teaches:

ANTIGENE ACTIVITY

The ability of PNA to cause transcription elongation arrest imply a very interesting potential for PNA as gene targeted drugs at the dsDNA level, especially since oligonucleotide triplex formation is not able to arrest RNA polymerase unless the oligonucleotide is modified in a way that allows a covalent crosslink to the target to be formed (34-36). However, **another aspect apart from the cellular uptake issue has to be considered before this may be reality.** As mentioned earlier, strand displacement binding of PNAs Tlo, T4CT5, or T4CT2CT2 to dsDNA is inhibited at

Na+ concentrations above 50 mM (26, ***31)*** and thus presumably also at physiological conditions in the cell nucleus (although this has not been investigated). **Therefore, PNAs with the propensity of binding to dsDNA under in vivo conditions should be investigated.**

. . .

PROSPECTS

It should be clear from the above presentation t h a t **the development of PNA and the investigation of its physicochemical and biological properties is only in its infancy and that much work is still required to assess if it will be able to bear fruit in terms of new gene targeted drugs** and reagents and give new insight into the physical and biological properties of DNA and maybe even evolution.

B. Hyrup et al. (1996) (Inventor Nielsen co-author) teaches:

5. PNA as a Potential Antisense and Antigene Drug

The potential use of PNA as an antisense or antigene drug for sequence-specific modulation of gene expression has bright prospects. However, several issues must be addressed before reaching this ultimate goal. In vitro assays examining the effect of PNA on replication, transcription and translation all look very promising.[34,35,50,51] Low concentrations of PNA are sufficient to obtain the desired effects, the sequence specificity is high and, furthermore, the biological stability of PNA appears to be sufficient for the application of PNA as a drug.[14] The drawbacks include poor cellular uptake of PNA[52,53] and possibly the sensitivity of strand displacement complex formation to high salt concentrations. The cellular uptake may improve by attachment of lipophilic or other helper groups to PNA, by formation of PNA–DNA chimeras, or by the use of liposomes or other techniques for drug delivery. Moreover, the pharmacological properties of PNA have not been thoroughly investigated.

Page 20, right hand column-page 21, left hand column

The future prospects of PNA as a drug have still to be assessed. The poor cell permeability of PNA may indicate poor bioavailability, and issues like the pharmacological properties of PNA have to be addressed. It has been discussed that the high thermal stability of PNA–nucleic acid complexes could lead to decreased sequence specificity at physiological temperature.[54] While this concern is certainly legitimate, the use of shorter PNAs and/or backbone modified PNAs should allow the stability to be controlled.

The inventor's own teachings suggest that the utility of PNAs as pharmacological agents remained uncertain.

C. Basu et al. (1997) (page 482, first ¶, left hand column):

> PNA activity as an antisense agent has been demonstrated *in vitro* and by microinjecting individual cells in culture (8). Microinjection of PNAs into cells was necessary because of poor cellular uptake (9) which was found to be 10 times less efficient than uptake of phosphorothioates in a variety of mammalian cells (10). One of the primary requirements for an oligonucleotide analog to be successful as an antigene/antisense agent is for it to be taken up by the cells in reasonable quantity so that it can reach its target in sufficient concentration. Since the PNAs suffer from poor cellular uptake, they have not been developed as an antigene/antisense therapeutic agent. To alleviate this situation, a strategy was developed to improve cellular uptake as well as to target the PNAs to specific cell types.

D. Finally, Ganesh et al. (review reference, one of the authors of which, P. Nielsen, is an applicant of this invention) teach that although peptide nucleic acids have been known since the beginning of the 1990's (i.e., time of filing the priority application of this application),

> ... some, but surely not all, of the promises expected from this molecule has materialized. Most success, has been achieved within diagnostic use of PNA oligomers in hybridization and PCR. The development of PNA oligomers into gene therapeutic drugs is still in its infancy. (p. 931)

Ganesh et al acknowledge that progress in the use PNAs as therapeutic drugs - in particular concerning cellular delivery - has been made only within the past couple of years (and refers to publications of years 1999-2000).

The same is discussed in the Background Section of US 6,472,209 (i.e., the patent against which the interference is being provoked):

> The success of an oligonucleotide analog as an antigene or antisense agent requires that the oligonucleotide be taken up by cells in reasonable quantities such that the oligonucleotide reaches its target at a sufficient concentration. PNA oligomers, however, have low phospholipid membrane permeability (Wittung et al , FEBS Letters 365 27-29 (1995)) and have been reported to be taken up by cells very poorly (Hanvey et al., Science 258:1481-1485 (1992); Nielsen et al , Bioconjugate Chem. 5 3-7 (1994); Bonham et al , Nucleic Acids Res 23:1197-1203 (1995); Gray et al., Biochem Pharmacol 48 1485-1476 (1997)), which would appear to limit their potential uses in antigene and antisense approaches.

In addition, Summerton (US 5,142,047), while acknowledging that nucleic acid analogs with uncharged backbones "have a potential" for enhanced rate of passage across cell membranes, expresses concern that

> There are, however, a variety of problems inherent in the structures of uncharged polynucleotide analogs of the type mentioned above. The structures are unstable in aqueous solution, do not allow assembly of different subunits in a defined order; and/or, the base-pairng moieties are not properly spaced for efficient binding to a target sequence.

Furthermore, Summerton teaches that configuring a polymer for inactivating target genetic sequences intracellularly may require conjugation to a carrier to favor its cellular uptake (col. 24, top).

Also, in addition, applicant previously argued that the publication of Hanvey et al. supports the enablement of the instant invention. It is reiterated here that microinjection administration, as addressed in Hanvey, does not read on *in vivo* treatment addressed in the instant claims. First, injection directly into nucleus of a cell can hardly be considered as "extracellular administration" addressed in the instant claims. Second, microinjection in general is not viewed as a method of *in vivo* administration.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art, one skilled in the art at the time the invention was made could not make and/or use the invention with the claimed breadth without an undue amount of experimentation. The skilled practitioner would first turn to the instant specification for guidance in practicing the full scope of the claimed method, however the specification only provides guidance to limited *in vitro* applications. As such, the practitioner would turn to the prior art for such guidance, however the prior art, at the time the invention was made, also lacked knowledge on how to produce *in vivo* effects on intracellular nucleic acid targets by extracellular administration of PNAs, at least in a "naked", un-conjugated form.

Finally, said practitioner would turn to trial and error experimentation to discover conditions of an *in vivo* administration without guidance from the specification or the prior art. Such represents undue experimentation.

Further, with respect to claims 38,43,53,61,70 drawn to "modification" of polypeptide expression, while the instant specification provides support for inhibition of protein expression, it does not provide support for any other modification (e.g., stimulation) of polypeptide expression.

Response to arguments

Applicant argues that "none of these publications indicates that the compounds do not produce at least some measurable level of the claimed biological response". To respond to this double-negative statement (emphasis added), it seems that the applicant rather than to point out at the evidence of the presence of the effect of PNAs prefers to point out at the absence of acknowledgement of the absence of effect. The point of the rejection is that with the lack of teaching in specification regarding *in vivo* delivery of PNAs into cells, much less of delivery of agents other than PNAs (i.e. those selected from a broad genus of "polyamide nucleic acid oligomers"), prior art also fails to provide guidance on how to achieve the effect t as claimed. In addition, as addressed in the rejection, applicant's own publications, published long after the effective filing date of the instant application, emphasize the unpredictability of the art.

With regard to discussing enablement demonstrated in US 6,472,209 ("Richelson patent over which applicant attempts to provoke interference), the reference is not considered because they are of post-filing date and enablement sufficiency of a specification is determined as of its filing date. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986). See MPEP 2164.05(a):

Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i e , the subject matter to which the claimed invention pertains The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed.

Suggesting an interference

At the time of filing, applicant suggested an interference with Richelson (US 6472209).

At the current stage of prosecution, there is no interference count being considered in the instant case as there no claims deemed allowable. Further, the interference has not been properly provoked in the instant

case, even though, originally, the instant claims are copied from Richelson (now the claims are amended).

To reiterate the record, at the time of filing applicants stated:

> In their claims 34-47, Applicants have copied claims 1, 2, 5, 10, 16-19, 24, 32-34, 43 and 52 of U S Patent No 6,472,209, issued on October 29, 2002. Other added claims are at least directed to substantially the same subject matter as claims that issued in U.S. Patent No 6,472,209 Since this amendment is being filed prior to October 29, 2003, Applicants have complied with the requirements of 35 USC § 135(b)(2) as well as 37 CFR 1 604(b).

Applicant's citation to 37 CFR 1.604(b) is in error. Since applicant was seeking to provoke an interference between a patent and an application, the application was subject to 37 CFR 1.607.

It is noted that the rules regarding interferences have changed since applicant's original filing and that 37 CFR 41.202 now applies:

> ***§ 41.202 Suggesting an interference.***
>
> (a) *Applicant* An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must
>
> (1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,
>
> (2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,
>
> (3) For each count, provide a claim chart companng at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),